

REMARKS

Reconsideration of this application is respectfully requested.

In the Office Action, the Specification was objected to under 35 U.S.C. §132 and claims 22 and 23 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting, rejected under 35 U.S.C. §112, first and second paragraph and 102(b). New claims 24-31 have been added. Support for claims 24-31 can be found in the specification. Claims 22 and 23 are pending in this application and are at issue.

The issues raised by the Examiner are summarized and addressed below.

INFORMATION DISCLOSURE STATEMENT

As requested by the Examiner, attached hereto as Exhibit 1 is a clean copy of Form PTO-1449 that is directed to the above-identified application which is a listing of references that have not been previously initialed, signed and dated.

OBJECTION TO THE SPECIFICATION UNDER 35 U.S.C. §132

The Examiner has objected to the Preliminary Amendment filed September 23, 2000 under 35 U.S.C. §132 because it allegedly introduced new matter into the disclosure. The added material which allegedly was not supported by the original disclosure was as follows: "EcoR digest of purified ... and for 2 months" which is inserted at page 5, line 18 after "1989". This was the definition of "stringend hybridization conditions" disclosed in Southern in *J. Mol. Biol.* 1998: 503, 1972. The Examiner alleged that the Southern article (a) did not define "stringent conditions" and (b) one would not be directed to select the particular specific conditions as compared to any of the other numerous examples of specific hybridization conditions set forth by Southern. This objection is respectfully traversed and reconsideration is respectfully requested.

Applicant respectfully submits that the amendment to the Specification was proper and do not constitute new matter. In maintaining her rejection, the Examiner has repeatedly stated that the Southern article describes multiple hybridization conditions, none of which are defined as

"stringent hybridization conditions". This was addressed in the Declaration by Dr. Crothers where he stated

"The fact that the Southern publication does not refer to these hybridization conditions as stringent conditions is not an indication of lack of stringency. Although the term was known in 1972 at the time of the Southern publication, it was not in common use until after 1975. Nevertheless, the concept of stringency (i.e., the concept that the intrinsic specificity of the hybridization reaction depends on the annealing conditions employed), was familiar to those of ordinary skill in the field. I am confident that, in 1993, a person of ordinary skill in the field would have recognized the hybridization conditions as disclosed in the Southern publication as what we would now call (and did call in 1993) stringent conditions."

The Examiner stated that the statement of Dr. Crothers that any set of conditions set forth in the Southern article would have resulted in selection of a hybrid between a nucleic acid of interest to an investigator and its complement was not persuasive because it presented an unsubstantiated conclusion and "Further, it appears to argue that any hybridization conditions are considered "stringent". However, in his Declaration, Dr. Crothers has pointed to specific segments of the Southern publication which disclose stringent conditions. For example, Figure 5 of the Southern article shows that hybridization was maximum at 80°C for the salt concentration of 6XSSC where as Figure 6 details that 80°C was chosen as the appropriate temperature for hybridization in 6XSSC. The legend to Plate II on page 508 discloses the condition of 1XSSC and 65°C which Dr. Crothers acknowledges as another stringent condition. Dr. Crothers also indicated that Southern stated that 65°C and 2XSSC were also stringent. Thus, the Examiner's statement is not true. Only a limited number of conditions were said to be stringent.

As mentioned above, the Examiner has termed the statement of Dr. Crothers "... all of the hybridization conditions set forth in the Southern Publication are stringent hybridization conditions and any set of the disclosed conditions would have resulted in the selection of a hybrid between a nucleic acid of interest to an investigator and its complement" (§ 7, Crothers Declaration) was not persuasive because it presented an unsubstantiated conclusion. However, Dr. Crothers' statements were based on his examination of the experimental conditions explored and used in the

Southern Publication. His expertise in these matters is evidenced in paragraphs 1 and 2 of his Declaration and his *curriculum vitae*, which detail his credentials. On the other hand, the Examiner has not presented any evidence supporting her position. In fact, Applicant respectfully submits that the Examiner has based her comments on a misreading of the Crothers Declaration.

The Examiner has argued that the present case is different from the "Hawkins" decisions, different from *In re Voss* 194 USPQ 144 (CCPA 1973) and *In re Fouche*, 169 USPQ 429 (CCPA 1071). The Examiner went on to say that in *In re Voss*, the Court cited *In re Seversky* 474 F.2d 671 177 USPQ 144 (CCPA 1973) where the requirements for incorporating references were clearly set forth. The Examiner stated that the incorporating statement must clearly identify the subject matter to be incorporated and where it is to be found. The Examiner concluded that in the instant case these requirements are not met by the specification passage of page 5, lines 15-20. Applicants respectfully disagree with the Examiner.

In *In re Hawkins* the reference simply stated "These novel compounds may for example be used in the production of valuable monomers for example by the processes described in copending British applications 36107/66, 42756/66, 46971/66, 49699/66, 50324/66, 10070/67, and 10071/67." *Hawkins*, 179 U.S.P.Q. at 159. The *In re Hawkins* reference consisted of string cites that were no more specific in terms of pointing to a chapter and verse within each cited reference, and due to their large number could be considered to be even less specific, than Applicant's reference to a single article in the present situation. Even so, the court found that a later amendment based on such a reference was "not new matter within the meaning of 35 U.S.C. § 135 . . ." because the information was "identified and specifically referred to for that information in the U.S. application as filed." *Hawkins*, 179 U.S.P.Q. at 162. Clearly, Applicant's incorporation of the Southern article "in its entirety" meets and exceeds the level of specificity found in *In re Hawkins*.

The Examiner asserted that the present situation is distinguishable from *In re Voss*, 194 USPQ 267 (CCPA 1973) and *In re Fouche*, 169 USPQ 429 (CCPA 1971). Again, Applicant respectfully disagrees with the Examiner's reading of these cases. The Examiner contended that the cases require incorporating statements that clearly identify the subject matter to be incorporated and

where it is to be found. However, the *In re Voss* court held that an earlier rejection, based on *In re Seversky* 474 F.2d 671, 177 USPQ 144 (CCPA 1973), confused two different concepts: "(1) the right to have the benefit of the filing date of an earlier application under [35 USC §] 120 ... and (2) the incorporation by reference in an application of matter elsewhere written down (not necessarily in a patent application), for economy, amplification, or clarity of exposition..." *Voss*, 194 USPQ at 270 (emphasis added). In *In re Voss*, the reference incorporated material only for the latter purpose: economy, amplification or clarity. Therefore a disclosure that stated "Reference is made to the United States Patent No. 2,920,971, granted S.D. Stookey, for a general discussion of glass-ceramic materials and their production" was held sufficiently specific without need for column and lines to allow later importation of material from the incorporated reference. *Voss*, 194 USPQ at 270. Similarly, in *In re Fouche*, the court held that "identification was reasonably precise," even though the "appellant could have used more precise identification technique ... [and] the technique used does not absolutely distinguish the application sought to be referenced from all other possible applications." *Fouche*, 169 USPQ at 431. As in the above cases, Applicant referenced "stringent hybridization" conditions in Southern for the purposes of economy, amplification, or clarity of exposition. Therefore, like *In re Voss* and *In re Fouche*, and unlike a situation where reference is made in order to claim the benefit of an earlier filing date, Applicant in the present situation need not reference to a specific page or paragraph. As a result, *In re Voss* and *In re Fouche* are directly on point and Applicant's reference to Southern in the present specification has at least the necessary specificity.

The Examiner has also misinterpreted the Crothers Declaration. The Examiner has taken the position that Dr. Crothers stated in his Declaration that the hybridization conditions in the Southern article only apply to the hybrid duplex disclosed therein and not to those in SEQ ID NO: 1 of the instant application. Dr. Crothers made a general statement that "It is generally found that this temperature occurs about 20° Celsius below the melting temperature of the hybrid duplex . . ." when referring to the temperature at which stringent hybridization occurs, and the Examiner stated that there was no indication of the melting temperature of the instantly claimed hybrid duplex. The Examiner concluded that Dr. Crothers stated that the selection of stringent hybridization conditions

was empirical in nature and not defined by the art. The Examiner also incorrectly stated that Dr. Crothers' Declaration emphasized the Examiner's position that stringent hybridization conditions are not art defined and are not defined in Southern but are empirical in nature. Applicant respectfully disagrees with the Examiner. Stringent hybridization conditions are a combination of temperature and salt concentration. Thus, the stringent hybridization conditions disclosed in the Southern article (e.g., 65°C, 1XSSC) and are not limited to the sequences disclosed therein. As the temperature increases, increasing amount of salt (e.g., SSC) must be used. At 65° C, 1XSSC is used. At higher temperatures e.g., 80°C, higher salt concentrations, 6XSSC, are used. Dr. Crothers stated this in his Declaration in paragraph 8 as follows:

"Southern used 65° C for hybridization in IX SSC, and showed the rate was maximum at 80° C for the higher salt concentration of 6XSSC as shown in Figure 5 of the Southern Publication."

The Examiner has also stated multiple times that Southern did not define any hybridization conditions as stringent and did not define the particular conditions of claim 23 as "stringent hybridization conditions." This was also addressed by the Crothers Declaration and it is stated on page 4:

"The fact that the Southern publication does not refer to these hybridization conditions as stringent conditions is not an indication of lack of stringency. Although the term was known in 1972 at the time of the Southern publication, it was not in common use until after 1975. Nevertheless, the concept of stringency i.e., the concept that the intrinsic specificity of the hybridization reaction depends on the annealing conditions employed, was familiar to those of ordinary skill in the field."

In terms of the Examiner's contention that Dr. Crothers' emphasized the Examiner's position that stringent hybridization conditions are not art defined and not defined in the Southern reference but are empirical in nature, Applicant respectfully submits that is not the case. Dr. Crothers stated:

"... I conclude that a person of ordinary skill in the art, at the relevant time, would have recognized that all of the hybridization conditions as set forth in the Southern publication are stringent hybridization

conditions and that any set of the disclosed conditions would have resulted in selection of a hybrid between a nucleic acid of interest to an investigator and its complement."

As evidence that "stringent hybridization conditions" are not empirical in nature and need not be independently determined for every different nucleic acid, Applicant respectfully submits that it can be seen in the Written Description Guidelines. In Example 9: Hybridization, it is stated:

"The art indicates that hybridization techniques using a known DNA as a probe under highly stringent conditions were conventional in the art at the time of filing."

Further on in the analysis it is stated:

"Now turning to the genus analysis, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim would yield structurally similar DNAs."

Thus, Applicant notes that stringent hybridization conditions are described as "conventional in the art" and there is no mention of the melting temperature of the hybrids.

The Examiner has stated that "stringency is defined by the "hybrid under study" and is empirical in nature and is defined by the structure of the hybridizing nucleic acid. One selects hybridization conditions to determine the extent to which the reaction conditions allow only completely complementary structures to form. As such, the nature and structure of the hybrid does in fact determine what is considered "stringent conditions or not.". The Examiner also stated "stringency is a term and concept of degrees and is not set forth nor discussed in Southern.". Applicant respectfully requests that the Examiner provide the references which form the basis of this opinion. If the statements are taken from the Declaration of Dr. Crothers, then Applicant respectfully submits that the Examiner is taking them out of context. In the absence of any outside reference, Applicant respectfully requests that the Examiner provide a declaration attesting to these facts.

Therefore, Applicant respectfully submits that the objection to the specification under 35 U.S.C. § 132 is not well taken and should be withdrawn.

Claims 22 and 23 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 26 and 28 of co-pending application No. 08/719,821. Applicant respectfully submits that a terminal disclaimer will be filed upon the indication of allowable subject matter in this case.

Claim 23 was also rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

This rejection is respectfully traversed and reconsideration is respectfully requested.

The Southern article has been incorporated by reference in its entirety. Therefore, these conditions, 65° C and 1XSSC salt concentration disclosed in claim 23, acknowledged by Dr. Crothers as stringent, were a part of this application since the effective filing date of the parent application. As mentioned above, Southern described multiple stringent hybridization conditions (e.g., 1XSSC, 65°C, 6XSSC, 80°C, 2XSSC, 65°C). The fact that Applicant claimed one condition is of no importance. Applicant is not required to claim everything that is disclosed in the specification.

Therefore, Applicant respectfully submits that the rejection is not well taken and should be withdrawn.

Claim 22 was also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite due to its recitation of "stringent conditions". The Examiner contended that "stringent conditions" was vague and indefinite, since no particular conditions were defined in the specification. This rejection is respectfully traversed and reconsideration respectfully requested.

Applicant respectfully submits that incorporation of the Southern reference in its entirety into the specification must mean that all of the hybridization conditions disclosed therein were a part of the specification as filed. As mentioned above, Dr. Crothers stated that those of ordinary skill in the art would recognize that the conditions disclosed in the Southern Publication are stringent hybridization conditions. Therefore, the term "stringent conditions" in claim 22 is fully supported by the specification.

Therefore, Applicant respectfully submits that the rejection of claim 22 under 35 U.S.C. § 112, second paragraph, is not well taken and should be withdrawn.

Claims 22 and 23 were also rejected under 35 U.S.C. § 102(b) as being anticipated by Sigma Molecular Biology Product Guide, 1991, pages 54-56. The Examiner contended that the reference teaches isolated purified oligo-d(pA) and oligo-d(pT) oligonucleotides and that each of the oligonucleotide products share a 100% identity with at least nucleotides 193-221 of SEQ ID NO:1. The Examiner concluded that these nucleic acids would hybridize under stringent conditions. The rejection is respectfully traversed and reconsideration is respectfully requested.

Applicant respectfully submits that the position that the Examiner is taking here is incompatible with her arguments above in the new matter objection and the Section 112, first and second paragraph rejections above.

The Examiner has gone to great lengths to state that stringent hybridization conditions are empirical in nature and depend upon the melting temperature of the hybrids. Applicant has disagreed and stated that these conditions are disclosed in the Southern article. However, neither the specific stringent hybridization conditions (e.g., 1XSSC and 65°C) nor the melting temperature of the hybrids obtained between oligo-d(pT) and residue numbers 193-221 of SEQ ID NO:1 is disclosed in the Sigma reference.

In making a rejection under Section 102(b), all of the elements of the claim must be present in a single reference. There is no disclosure in the Sigma reference to stringent or any hybridization conditions whatsoever.

Therefore, Applicant respectfully submits that the rejection so claims 22 and 23 under 35 U.S.C. § 102(b) is not well taken and should be withdrawn.

Claims 22 and 23 stand rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to the skilled artisan that the inventor had possession of the claimed invention at the time the application was filed. Specifically, it was noted that the claims are directed to isolated and purified nucleic acids that hybridize under stringent conditions or specific conditions. The Examiner has noted that SEQ ID NO:1 was a genomic DNA fragment and stated that the specification did not disclose that SEQ ID NO:1 was drawn to a full length open reading frame and specifically teaches that it is a fragment. The Examiner went on to say that claims reciting the "comprising" term read upon complete gene sequences having in common a nucleotide sequence of SEQ ID NO:1 from any source. The Examiner concluded that with the exception of a nucleic acid consisting of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, regardless of the simplicity of the method of isolation, absent further guidance. In addition, it was stated that since the claimed genus encompasses undisclosed genes, partial genomic sequences, and genes yet to be discovered, the disclosed structural feature (i.e., the nucleic acid consisting of SEQ ID NO:1) did not constitute a substantial portion of the claimed genus. The Examiner concluded that absent a written description disclosing a representative number of nucleic acid sequences from this broad class of polynucleotides, the specification failed to show that Applicant was "in possession of the claimed invention" at the time the application for patent was filed.

In addition, the Examiner contended that although the claims are drawn to a nucleic acid comprising a sequence which hybridizes under stringent conditions or specific stringent conditions to a nucleic acid comprising a sequence as set forth in SEQ ID NO:1, there did not appear to be an adequate written description in the specification as filed of the essential structural features of the instantly recited nucleic acids, nor a correlation between a particular structure and function. The Examiner also stated that it was because of the open language of the claims that the specification

failed to provide an adequate written description of the instant claims. This rejection is respectfully traversed and reconsideration is respectfully requested.

In making this rejection, the Examiner has contended that the specification did not disclose that SEQ ID NO:1 is drawn to a full length open reading frame and specifically teaches that it is a fragment. As explained further below, this is not the case. The sequence depicted in SEQ ID NO:2 is the complete open reading frame for the protein PvESP-1. Therefore, the specification as filed contains an adequate written description of the essential structural feature of the instantly recited nucleic acids and a correlation between a particular structure and a function. Therefore, SEQ ID NO:1 constitutes a substantial portion of the claimed genus and the specification contains an adequate written description.

Attached hereto as Exhibit 2 is a declaration from John W. Barnwell (the "Barnwell Declaration"), the inventor of the present application. In paragraph 6, on page 2, of the Barnwell Declaration, Dr. Barnwell declares that the sequence depicted in SEQ ID NO:2 is the complete open reading frame of PvESP-1. The sequence includes the amino acid translation of a clone showing an exon I encoding a classic signal peptide, a 140 bp intron, and an exon II encoding the remainder of the protein.

Further, in paragraph 7, on page 2 of the Barnwell Declaration, Dr. Barnwell states that the complete gene codes for 1011 amino acids with a calculated molecular weight of 112,752 Da. The molecular mass of the native protein as estimated by SDS-PAGE is 220-225 kDa and that of the recombinant protein expressed in *E. coli* by the plasmid is 205-210 kDa. Thus, there is a discrepancy between the molecular weights of the native and recombinant protein, as well as a discrepancy between the calculated molecular weight and that observed by SDS-PAGE. Dr. Barnwell explains both of these observations in paragraphs 8-9, on pages 2-3, of the Barnwell Declaration. First, in paragraph 8, on pages 2-3, of the Barnwell Declaration, Dr. Barnwell provides various explanations for the small apparent discrepancy between the molecular weights of the native and recombinant proteins. He explains that this may be due to the inability of the bacteria to splice introns, additional *in situ* proteolysis of the expressed protein, or post-translational modification. In

paragraph 9, on page 3, of the Barnwell Declaration, Dr. Barnwell also explains the discrepancy between the calculated molecular weight of the native protein and that observed by SDS-PAGE. Specifically, Dr. Barnwell states that such discrepancies are common among *Plasmodium* proteins because they contain repeated proline rich amino acid motifs that introduce rigidity into the structure of the proteins, making them less susceptible to denaturation by SDS. Therefore, the proteins are not well separated by the gel matrix and their molecular weight cannot be accurately determined by SDS-PAGE.

Therefore, as shown in the Barnwell Declaration, it is evident that the sequence contained in SEQ ID NO:2 of the instant specification is the complete open reading frame of PvESP--1.

Applicant respectfully submits that the instant specification enables the complete open reading frame of PvESP-1, as evidenced by the disclosure, and particularly by the examples. Example 2 describes how a *P. vivax* expression library was screened with monoclonal antibodies specific for PvESP-1 and PvESP-2. One of the antibodies, mAB 1D11.G10 specifically recognized one recombinant phage plaque, which was then purified and excised to yield a plasmid containing a 3.34 kb insert. Example 3 shows how the plasmid was transformed in *E. coli* and expression was induced. The proteins expressed by these clones were probed with monoclonal antibodies specific for PvESP--1 and PvESP--2, which revealed a protein of approximately 205-210 kD by SDS-PAGE. The insert was sequenced by the methods described in Example 4, and the entire PvESAP--1 gene sequence was found, as set forth in SEQ ID NO:1, as well as the deduced protein sequence set forth in SEQ ID NO:2.

Example 8 of the Written Description Guidelines relates to the disclosure of a DNA fragment encoding a full open reading frame. In that example, the specification discloses a sequence isolated and sequenced from a cDNA library, identified by SEQ ID NO:2. The specification teaches that the complete open reading frame provided in SEQ ID NO:2 encodes SEQ ID NO: 3, and an alignment of SEQ ID NO:3 with known amino acid sequences of DNA ligases shows a high level of sequence similarity between SEQ ID NO:3 and the consensus sequence of

Finally is the issue that Applicant mischaracterized the sequence set forth in SEQ ID NO:2 as a fragment. According to the decision in *Wahl Instruments, Inc. v. Acvious*,¹ a misrepresentation in a patent specification will only defeat the enablement of an invention if the skilled artisan fails to recognize the mistake and relies on it to practice the invention. In the instant case, whether the skilled artisan recognizes the misstatement in the disclosure is of no moment; rather, if the skilled artisan reduces the invention to practice according to the explicit instructions provided in the specification, he or she will inevitably derive the full open reading frame of PvESP--1, as shown in SEQ ID NO:2. Thus, the disclosure is enabling for the full scope of the claimed invention, despite the inadvertent mischaracterization of the sequence set forth in SEQ ID NO:2 as a fragment.

Therefore, because the specification discloses the full open reading frame of PvESP--1, in accordance with the guidelines discussed above, Applicant is entitled to claims directed to nucleic acids comprising the sequence of SEQ ID NO:1. The claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO:1 and must encode a protein with a specific function. It has been found that a search of the prior art indicated that SEQ ID NO:1 is novel and unobvious. There is a single species disclosed that is within the scope of the claimed genus (a molecule consisting of SEQ ID NO:1) and there is actual reduction to practice of the disclosed species. Therefore, Applicant respectfully submits that a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Therefore, a representative number of species is disclosed, since stringent hybridization conditions in combination with the coding function of the DNA and the level of skill and knowledge in the art are adequate to determine that Applicant was in possession of the claimed invention.

Therefore, the skilled artisan would recognize from the disclosure that Applicant was in possession of the genus of nucleic acids which comprise SEQ ID NO:1.

¹ 950 F.2d 1575, 21 USPC2d 1123 (Fed. Cir. 1991).

Therefore, Applicant respectfully submits that the rejection of claims 22 and 23 under 35 U.S.C. § 112, first paragraph, is not well taken and should be withdrawn.

In view of the above, pending claims 22 and 23 in this application are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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